(p-carboxyphenoxy) hexane (CPH) copolymers in a ratio of about 20:80, an immunogenic protein or proteins of Influenza A Virus, Influenza B Virus, Influenza C Virus, or Influenza D Virus, and an adjuvant, each of the immunogenic proteins and adjuvant entrapped within an interior of the nanoparticle, and an excipient.

Other preferred immunogenic compositions include at least a second biodegradable polyanhydride nanoparticle having at least a second immunogenic protein of an Influenza Virus and an adjuvant within an interior of the second nanoparticle. However, the second immunogenic protein(s) may be different than the immunogenic protein(s) in the first nanoparticle.

Preferably, the immunogenic protein includes one or more of Hemagglutinin (HA), Neuraminidase (NA), Nucleocapsid Protein (NP), Matrix Protein 1 (M1), Matrix Protein 2 (M2), Polymerase Basic Protein 1 (PB1), Polymerase Basic Protein 2 (PB2), Polymerase Acidic Protein (PA), Nonstructural Proteins 1 (NS1), Nonstructural Proteins 2/Nuclear Export Protein (NS2/NEP), Polymerase Basic Protein 1 Segment Second Proteins (PB1-F2), Influenza B Virus Membrane Protein (BM2), Influenza B Virus Membrane Protein (NB), Influenza A Virus Segment 2 Alternative Splicing Protein (M42), Influenza A Virus Segment 1 Alternative Splicing Protein (PB2-S1), Influenza A Virus Segment 2 Alternative Initiation Protein (N40), Influenza A Virus Segment 3Ribosomal Shift Protein (PA-X), Influenza A Virus Segment 3 Alternative Initiation Protein (PA-N182), Influenza A Virus Segment 3 Alternative Initiation Protein (PA-N155), Influenza C/D Virus Polymerase Complex Protein (P3), Influenza C/D Virus Surface Glycoproteins: Hemagglutinin, Esterase, and Fusion activities (HEF), Influenza C/D Virus Matrix Protein (CM1), or Influenza C/D Virus surface glycoprotein CM2.

Certain embodiments of the invention include one or more immunogenic proteins of an Influenza A virus subtype H1, H2, H3, H5, and H7. In other preferred embodiments, the immunogenic proteins may include one or more of Influenza A Virus HA subtypes H1 and H3; Influenza A Virus NA subtypes N1 and N2; Influenza A Virus NP; Influenza A Virus M1; and Influenza B Virus HA and NA. In still further preferred embodiments, immunogenic proteins may include Influenza A Virus HA subtypes H1 and H3; Influenza A Virus NA subtypes N1 and N2; and Influenza A Virus NP, M1, NS1, PA, and PB1; Influenza A Virus HA subtypes H5 and H7, and H9; Influenza A Virus NA subtypes N1, N2, N7, and N9; and Influenza Virus A NP and M1.

Certain preferred embodiments of the invention may include an immunogenic composition in which the polyanhydride nanoparticle comprises by weight about 2.5% HA, about 2.5% NP, and about 2% CpG polynucleotide. Other preferred embodiments of the invention include also polyanhydride nanoparticle comprising by weight about 1% HA, about 1% NP, and about 2% CpG polynucleotide or about 1% HA, about 1% NP, and about 2% R848.

In certain embodiments, the adjuvant may include a Toll-Like Receptor (TLR) agonist, a liposome, a mineral salt, an oil emulsion, a polymer, a polysaccharide, a saponin, R848, or a STING activating adjuvant. Embodiments also may include a second adjuvant in the excipient that may be the same or different than the adjuvant entrapped within a nanoparticle.

Certain preferred embodiments of the invention include a targeting protein disposed on at least a portion of a surface of a nanoparticle that may direct the nanoparticle to a specific cell type. For example, the targeting protein may be an antibody or ligand that specifically binds to CLEC9a, Dectin-1, SIRpa, or MERtK.

Embodiments of the immunogenic composition disclosed herein may be administered to a subject through various delivery routes. Preferably, an immunogenic composition may be delivered intranasally, intramuscularly, subcutaneously, or a combination thereof.

Embodiments of the invention provide several advantageous over the prior art. Most notably, embodiments of the invention allow a user to design an immunogenic composition that may utilize or a take advantage of tissue-specific factors and critical pathways for induction of tissue-specific T and B cell immunogenic response to generate local and systemic immunity.

Advantageously, embodiments of the invention may provide a universal protection against multiple homologous and heterologous strains of influenza virus without any toxicity related to natural influenza virus infections.

Advantageously, embodiments of the invention may be administered intranasal to facilitate immunity in both the upper and lower airway including the formation of local resident T and B memory cells.

Advantageously, the bioerodible or biodegradable properties of the nanoparticles allow for a sustained release of an entrapped immunogen and adjuvant to act as a long-term immunogen depot.

Advantageously, certain embodiments of the invention may induce full adaptive immunity (antigen-reactive B cells, antibody (Ab), CD4 T cells, CD8 T cells) and protection against influenza challenge (both homologous and heterologous) after intranasal (i.n.) administration of immunogenic composition in both the presence and absence of a free antigen component in the excipient.

The present invention and its attributes and advantages will be further understood and appreciated with reference to the detailed description below of presently contemplated embodiments, taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the specification and are included to further demonstrate certain embodiments or various aspects of the invention. In some instances, embodiments of the invention can be best understood by referring to the accompanying drawings in combination with the detailed description presented herein. The description and accompanying drawings may highlight a certain specific example, or a certain aspect of the invention. However, one skilled in the art will understand that portions of the example or aspect may be used in combination with other examples or aspects of the invention.

FIG. **1** illustrates vaccination with IAV-nanovax induces lung-resident germinal center B cell responses. C57BL/6 mice were challenged i.n. with a 110 tissue culture infections unit (TCIU) of A/Puerto Rico/8/1934, vaccinated i.m. with IIV, prime+boost vaccinated i.n. with IAV-nanovax (Nanovax) or left unchallenged/unvaccinated (naïve). At 32 and 45 days post challenge/vaccination, (A, D) lung-resident B cells, (B, E) germinal center (GC) B cells, and (C, F) class switched B cells were enumerated within the lungs. Error bars mean±s.e.m. Data are from two pooled experiments (A, B, C; n=8 mice/group) or one (D, E, F; n=4 mice/group) independent experiment. **P<0.01, ***P<0.001, ****P<0.0001 (One-way ANOVA with Tukey's multiple comparisons test).